-- 66. A protein consisting of a grafted optimized protein surface loop that specifically binds a selected target, wherein the protein surface loop is not endogenous to the protein, replaces a surface loop on the protein, and the protein is selected from the group consisting of an enzyme, a thrombolytic agent, an anticoagulant, an apoptotic protein, a growth factor, a cytokine, and a cell surface receptor ligand. --

Please cancel claims 1 and 4-12 without prejudice.

REMARKS

Claims 1, 3-24 and 65 are pending in the present application. Claims 3 and 13-24 are amended herein for clarity and to more particularly define the invention. Support for these amendments can be found in the language of claims 3 and 13-24 as originally filed. Claims 1 and 4-12 are canceled herein without prejudice. New claim 66 is added herein. Support for this new claim can be found on page 13, lines 1-21. It is believed that no new matter has been added by these amendments or this new claim. In light of these amendments and the following remarks, applicants respectfully request reconsideration of this application, entry of these amendments and the new claim and allowance of the pending claims to issue.

Applicants wish to thank Examiners Chan and DiBrino for taking the time to participate in a telephone interview on January 9, 2001 with Dr. Jeffrey Smith, Dr. Mary Miller and Dr. Lizette Fernandez to discuss the pending claims. During this telephone interview, the Paoni et al. reference and the rejection under 35 U.S.C. § 103 were discussed. The following remarks address the specific rejections under 35 U.S.C. § 102 (b) and 35 U.S.C. § 103 (a) in the context of this discussion.

I. Oath or declaration

The Office Action states that a new oath or declaration in compliance with 37 C.F.R. 167(a) identifying this application by application number and filing date is required. The oath or declaration is allegedly defective because: 1) the declaration lists the filing date as 6/19/98, whereas the filing date of the instant application is 10/6/98; 2) the declaration states that filing was with amendments through November 17, 1998, whereas the filing date of the preliminary amendment is November 24, 1998; 3) the declaration allegedly claims priority to PCT/US96/20577 under 35 U.S.C. § 119a-d and that the priority claim should be made under 35 U.S.C. § 120.

Applicants respectfully pointed out to the Examiners during the January 9, 2001 telephone interview that the Declaration provided with the Amendment filed on May 14, 2000 identifies the application by application number and that there is no requirement under 37 C.F.R.

§ 1.63 that the application must be identified by filing date. Furthermore, applicants provide herein a Certificate of Mailing under 37 C.F. R. § 1.8 showing that the preliminary amendment was filed on November 17, 1998. Applicants also point out that it is stated on the Declaration that this application claims priority to PCT/US96/20577 under Title 35, United States Code §119 (a)-(d) or §365(b) of any foreign application(s) for patent or inventor's certificate, or §365(a) or §365(b) of any PCT international application which designated at least one country other than the United States of America. Therefore, applicants believe the Declaration filed on May 14, 2000 has been properly submitted without defects and respectfully request withdrawal of this objection.

II. Rejection under 35 U.S.C. § 112

The Office Action states that claims 1 and 4-24 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Specifically, the Office Action states that the instant claims encompass an agent comprising an isolated peptide mimetic and that a peptide mimetic is disclosed in the specification to " include a chemical compound, or an organic molecule or any other peptide mimetic, the structure of which is based on or derived from a binding region of a protein." The Office Action then states that there is insufficient relevant identifying structural characteristics disclosed by the instant specification for which

chemical compounds or organic molecules other than proteins or peptides are peptide mimetics that bind a selected target.

As stated above, claims 1and 4-12 are canceled herein without prejudice. Claims 13-24 are amended herein to no longer depend from claim 1. Thus, applicants believe that this rejection has been overcome and respectfully request its withdrawal.

III. Rejection under 35 U.S.C. § 102(b)

The Office Action states that claims 1, 3-13, 15-16 and 65 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Paoni et al. (*Protein Eng.* Vol. 6, 1993, pages 529-435) as evidenced by Gething et al. (*EMBO Journal* Vol. 7, 1988, pages 2731-2740).

Specifically, the Office Action states that Paoni et al. teaches a targeted therapeutic agent comprising a therapeutic functional entity (tPA) linked to an optimized surface loop (amino acid residues EIHPV of vampire bat tPA) that binds to a selected target (fibrin). According to the Office Action, Paoni et al. teaches that the entity is loop-grafted tPA. Claim 4 is included because the term "medical or diagnostic device" encompasses tPA, which can function in thrombolysis. Claim 8 is included because tPA is an enzyme as evidenced by Gething et al. The Office Action also states that the term "grafted" is not disclosed in the instant specification.

Claims 1 and 4-12 are canceled herein without prejudice. Claims 13 and 15-16 are amended herein to no longer depend from claim 1, thus rendering this rejection moot as it pertains to those claims.

As discussed at length during the January 9, 2001 telephone interview, applicants respectfully point out that the Paoni et al. reference does not teach a therapeutic agent consisting of a grafted optimized protein surface loop that specifically binds to a selected target. Specifically, Paoni et al. describes site-directed mutagenesis of amino acids 466-470 of tPA, which results in the replacement of amino acids 466-470 of tPA with amino acid residues EIHPV of vampire bat tPA. This reference clearly states that the amino acids at positions 466-470 define a previously uncharacterized loop structure (page 529, second paragraph). Paoni et al. also states that "residues 466-470 are part of another loop structure for which there is no homologous region on chymotrypsin. To our knowledge no function has been described for this region." (Page 532, column 2, second full paragraph). Therefore, no binding function is ascribed to this loop region and no binding data are presented to show that amino acids 466-470 bind to <u>any</u> target, much less fibrin. Furthermore, there is no evidence in the Paoni et al. reference that the mutagenized tPA, comprising amino acid residues EIHPV of vampire bat tPA, binds to a selected target, i.e. fibrin.

Furthermore, although Paoni et al. describes increased fibrin specificity, the fact that increased fibrin specificity is still observed when amino acid residues 466-470 are deleted from

tPA indicates that increased fibrin specificity is not and could not be due to increased binding of this loop to fibrin (see Figure 6). In fact, Paoni et al. evaluates the potential for additivity of fibrin specificity with these amino acid variants by dividing the activity relative to wild type tPA in the fibrin-stimulated assay by the relative activity in the fibrinogen-specific assay (page 532, column 2, first full paragraph). Thus, fibrin specificity is defined by a ratio of specific activities in the presence of two different cofactors, which does not take into account any binding effect. Paoni et al. also describes an increase in fibrin specificity of tPA by reducing fibrinogen-stimulated activity (page 532, column 2, third full paragraph), not by increasing its binding affinity for fibrin.

Therefore, not only do amino acid residues 466-470 of tPA have no known binding function, but no optimization of binding function occurs upon replacement of these residues with EIHPV of vampire bat tPA and there is no evidence of the EIHPV vampire bat tPA loop binding a selected target. Therefore, one of skill in the art would readily conclude, from the teachings of the Paoni et al. reference, that amino acid residues 466-470 of tPA have not been optimized to increase its natural affinity for a target binding site by replacing these residues with EIHPV of vampire bat tPA. Thus, applicants believe that the present rejection has been overcome and respectfully request its withdrawal as it pertains to claim 3 and its dependent claims 13-24 and 65.

III. Rejection under 35 U.S.C. § 103(a)

The Office Action states that claims 1 and 3-24 are rejected under 35 U.S.C § 103(a) as allegedly being unpatentable over Bode et al. (*Circulation*, Vol. 84, 1991, pages 805-813) in view of Smith et al. (*J. Biol. Chem.* Vol. 269, 1994, pages 32788-32795) and further in view of Barbas et al. (*PNAS*, Vol. 90, 1993, pages 10003-10007), Todd et al. (Clinical Diagnosis and Management by Laboratory Methods, 1979, Vol. 1, page 252) and Johannessen et al. (*Thrombosis and Haemostasis*, Vol. 63, 1990, pages 54-59).

Specifically, the Office Action states that it would have been *prima facie* obvious to one of ordinary skill in the at at the time the invention was made to have substituted the 7E3 antibody in the invention of Bode et al. with another high affinity monoclonal antibody specific for a platelet integrin, particularly one such as the MTF-10 antibody of Smith et al. One of ordinary skil in the art at the time the invention was made would have allegedly been motivated to do this in order to provide an antibody with high affinity to integrin which is present on platelets and with lower affinity to integrins on other cell types. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have substituted another type of plasminogen activator such as tissue plasminogen activator (t-PA) of Johannesen et al. for the plasminogen activator urokinase of Bode et al. in the invention of Bode et al., particularly in light of the teaching of Johannessen et al. of the high efficacy and specificity of t-PA and the need for increasing the circulatory half-life of t-PA administered by itself.

Claims 1 and 4-12 are canceled herein without prejudice and claims 13-24 are amended herein to no longer depend from claim 1, thus rendering this rejection moot as to those claims.

Applicants respectfully point out that if one skilled in the art were to combine the teachings of Smith et al. with those of Bode et al., the result would be a fusion protein (i.e., two distinct, large proteins fused together) and not a protein comprising a grafted optimized surface loop that binds to a selected target. Applicants also point out that a "surface loop," as defined on page 12, lines 19-21of the specification, is a flexible loop structure in the native protein of about 2 to about 20 amino acids. Therefore, an "optimized protein surface loop" is not an antibody such as the MTF-10 antibody disclosed in the Smith et al. reference or the Fab-9 antibody taught by Barbas et al., which are much larger proteins. One skilled in the art would not have been motivated to substitute an optimized surface loop for the 7E3 antibody of Bode et al. based on the teachings of Smith et al. or Barbas et al., because the entire MTF-10 antibody or the entire Fab-9 antibody would be necessary according to the teachings of Bode et al., not an optimized surface loop as claimed in the present invention.

Furthermore, claim 3 as amended herein recites a protein consisting of a grafted optimized protein surface loop that specifically binds a selected target, wherein the protein surface loop is not endogenous to the protein, replaces a surface loop on the protein, and wherein the protein is not an antibody. Therefore, since neither the protein nor the protein surface loop,

as defined in the specification, is an antibody, one skilled in the art would not be motivated to combine the teachings of Bode et al., Smith et al., Barbas et al., Todd et al. and Johannessen et al. to produce the present invention with any reasonable expectation of success. Applicants have demonstrated herein that there is no teaching or suggestion in Bode et al., Smith et al., Barbas et al., Todd et al. and/or Johannessen et al. of a protein consisting of a grafted optimized protein surface loop that specifically binds a selected target, wherein the protein surface loop is not endogenous to the protein, replaces a surface loop on the protein, and wherein the protein is not an antibody. Therefore, Applicants believe this rejection has been overcome as it applies to amended claim 3 and dependent claims 13-24 and 65, and respectfully request its withdrawal.

Furthermore, applicants respectfully point out that an antibody containing a complementarity determining region (CDR) from another antibody, or an antibody containing an optimized CDR loop which specifically binds a selected target (Barbas et al.), differs from the present invention, which claims a non-antibody protein consisting of a grafted optimized surface loop. One might expect some degree of success in grafting loops into antibodies because antibodies, unlike other proteins, have evolved to recognize millions of diverse antigens. Such recognition is accomplished via the VDJ gene rearrangements in the antibody repertoire. These gene rearrangements lead to the presentation of many different combinations of CDRs in the context of a common IgG framework. Since the antibody molecule has evolved to accept vast numbers of CDR loops of varying sequence and varying structure, the replacement of a CDR

loop with a CDR loop from another antibody, or the optimization of a CDR loop in an antibody is possible without altering the overall structure of the antibody. Yet, although antibodies possess a common IgG framework, the replacement of a CDR loop in one antibody (i.e., the recipient antibody) with a CDR loop from another antibody (i.e., the donor antibody), does not always result in selective binding of the recipient antibody to a desired, new target site. Therefore, knowing that CDR swapping between antibodies, which have nearly identical structural properties, does not guarantee selective binding, and knowing that antibodies are unique in their ability to accommodate diverse loops in the antigen binding site, one skilled in the art could not anticipate success in loop grafting into proteins that are not antibodies. Therefore, one skilled in the art would not be motivated to place an optimized surface loop from one protein, into a new location on another structurally unrelated protein to make a protein consisting of a grafted optimized protein surface loop that specifically binds a selected target, wherein the protein surface loop is not endogenous to the protein, replaces a surface loop on the protein, and wherein the protein is not an antibody.

For these reasons, applicants contend that the claimed invention could not have been obvious from the teachings of the cited art, either alone or in combination. Thus, applicants believe this rejection has been overcome and respectfully request its withdrawal.

IV. New claim 66

New claim 66 recites a protein consisting of a grafted optimized protein surface loop that specifically binds a selected target, wherein the protein surface loop is not endogenous to the protein, replaces a surface loop on the protein, and the protein is selected from the group consisting of an enzyme, a thrombolytic agent, an anticoagulant, an apoptotic protein, a growth factor, a cytokine and a cell surface receptor ligand. Applicants believe that this new claim is free of the pending rejection under 35 U.S.C. § 102(b) because, for the reasons stated above, Paoni et al. do not teach a protein consisting of a grafted optimized protein surface loop that specifically binds to a selected target. Furthermore, applicants believe that new claim 66 would not have been obvious on the basis of the teachings of the prior art cited under 35 U.S.C. § 103(a) because, if the skilled artisan were to combine the teachings of the cited art, the result would be a fusion protein and not an enzyme, a thrombolytic agent, an anticoagulant, an apoptotic protein, a growth factor, a cytokine, or a cell surface receptor ligand consisting of a grafted optimized surface loop that binds to a selected target. Therefore, applicants believe that new claim 66 is neither anticipated by Paoni et al., nor rendered obvious by the teachings of Bode et al., Smith et al., Barbas et al., Todd et al. or Johannessen et al., either alone or in any combination. Therefore, applicants respectfully request entry and allowance of new claim 66.

Pursuant to the above amendments and remarks, reconsideration and allowance of the pending claims in this application is believed warranted. The Examiner is invited and

encouraged to directly contact the undersigned if such contact may enhance the efficient prosecution of this application to issue.

A check in the amount of $445.00 and a Request for an Extension of Time are enclosed. This amount is believed to be correct; however, the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner of Patents, Washington, D.C. 20231, on the date shown below.

Mary L. Miller — February 15, 2001
Mary L. Miller — Date